AMENDMENTS

In the Specification:

Please insert the attached "Sequence Listing" as separately numbered pages 1 - 4 after the abstract.

Please amend the paragraphs beginning on page 4, line 8 as follows:

Various suitable tag sequences are known in the art, including, for example, MRGS $(H)_6$ (SEQ ID NO: 1), DYKDDDDK (SEQ ID NO: 2) (FLAG™), T7-, S- (KETAAAKFERQHMDS) (SEQ ID NO: 3), poly-Arg (R_{5-6}), poly-His (H_{2-10}), poly-Cys (C_4) poly-Phe (F_{11}) poly-Asp (D_{5-16}), Strept-tag II (WSHPQFEK) (SEQ ID NO: 5), c-myc (EQKLISEEDL) (SEQ ID NO: 4), Influenza-HA tag (Murray, P. J. et al (1995) *Anal Biochem* 229, 170-9), Glu-Glu-Phe tag (Stammers, D. K. et al (1991) *FEBS Lett* 283, 298-302), Tag. 100 (Qiagen; 12 aa tag derived from mammalian MAP kinase 2), Cruz tag 09™ (MKAEFRRQESDR, Santa Cruz Biotechnology Inc.) (SEQ ID NO: 6) and Cruz tag 22™ (MRDALDRLDRLA, Santa Cruz Biotechnology Inc.) (SEQ ID NO. 7). Known tag sequences are reviewed in Terpe (2003) Appl. Microbiol. Biotechnol. 60 523-533.

In preferred embodiments, a poly-His tag such as MRGS (SEQ ID NO: 1) $(H)_6$ is used.

Please amend the paragraphs beginning on page 5, line 1 as follows:

In some preferred embodiments, a rhomboid cleavable TMD may have a lumenal portion which has the same conformation within the membrane as Spitz (Q01083) residues 140-144 (IASGA) (SEQ ID NO: 8) or more preferably Spitz residues 138-144 (ASIASGA) (SEQ ID NO: 9), or the equivalent residues in a different rhomboid ligand, such as Gurken (P42287), Keren (AAF63381), Mgml (YOR211C), Ccpl (YKR066C) or mammalian thrombomodulin, for example mouse thrombomodulin (NP033404), rabbit (Oryctoclagus cuniculus; AAN15931); rat (Rattus norvegicus; NP~113959), cow (Bos Taurus ; AAA30785) or human thrombomodulin (AAH533357). Other rhomboid ligands include EGFR ligands, examples of which are shown in Table 2.

The lumenal portion of a rhomboid cleavable TMD may, for example, comprise or consist of Spitz residues 140-144 (IASGA) (SEQ ID NO: 8), more preferably Spitz residues138-144 (ASIASGA) (SEQ ID NO: 9), or the equivalent residues in a different rhomboid ligand, such as Gurken, Keren, Mgml, Ccpl or thrombomodulin.

Please amend the paragraph beginning on page 9, line 25 as follows:

The rhomboid polypeptide may comprise an ER (endoplasmic reticulum) retention signal. The KDEL (SEQ ID NO: 10) ER retention signal is not found in natural rhomboid polypeptides and directs the expressed rhomboid polypeptide to be retained in the ER (endoplasmic reticulum) rather than the Golgi apparatus.

Please amend the paragraph beginning on page 13, line 15 as follows:

One class of putative inhibitor compounds can be derived from a Rhomboid polypeptide and/or a rhomboid ligand TMD. Membrane permeable peptide fragments of from 5 to 40 amino acids, for example, from 6 to 10 amino acids may be tested for their ability to disrupt such interaction or activity. Especially preferred peptide fragments comprise residues 141 to 144 (ASGA) (SEQ ID NO: 11) of the Spitz protein, residues 140-144 (IASGA) SEQ ID NO: 8) or residues 138-144 (ASIAGA) (SEQ ID NO: 9), or the equivalent regions of other rhomboid ligands.

Please amend the paragraph beginning on page 16, line 32 as follows:

A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be grafted. The template molecule and the chemical groups grafted on to it can conveniently be selected so that the modified compound is easy to synthesise, is likely to be pharmacologically acceptable, and does not degrade in vivo, while retaining the biological activity of the lead compound. Modified compounds found by this approach can then be screened to see whether they have the target property, or to what extent they exhibit it. For example, mimetics which model the three-dimensional conformation of the Rhomboid recognition domain of a rhomboid ligand (for example, Spitz residues 140-144: IASGA (SEQ ID NO: 8), or more preferably residues 138-144: ASIASG (SEQ ID NO: 9)) may be used to screen

for a compound which binds and inhibits a Rhomboid polypeptide. Such mimetics may include peptide chloromethyl ketone analogues of the Rhomboid- binding domain of a rhomboid ligand, for example, a Spitz analogue comprising the IASGA (SEQ ID NO: 8) or ASIASGA (SEQ ID NO: 9) sequence.

Please amend the paragraphs beginning on page 23, line 27 as follows:

To replace the GFP reporter and TGFα signal sequences with SEAP, the SEAP gene and signal sequence was amplified by PCR using the primers "HindSEAP For" (5'-AAGCTTCACCATGCTGCTGCTGCTGCTGCTGCT-3') (SEQ ID NO: 12) and "Eco Back"(5'-ACGGAATTCTGTCTGCTCGAAGCGGCCGGC-3') (SEQ ID NO: 13) and pSEAP-2 template DNA (Clontech). The product was cloned into GFP/TGFα/Spi/TGFα using *Hind*III and *Eco*RI restriction sites to generate SEAP/TGFα/Spi/TGFα (construct b, fig. 1).

To prepare the constructGFP/6H/Spi/TGFα (construct c, figure 1), PCR primers were designed to amplify the SPITZ TMD and to introduce the MRGS $(H)_6$ tag sequence immediately upstream. The primers"6HMRGS For"(5'-CGGAATTCATGAGAGGATCGCATCACCATCACCATCACGCGAGCATTGCCAGTGGAGCCA-3') (SEQ ID NO: 14) and "BBS Back" (5'-CTGCTATTGTCTTCCCAATCCT-3') (SEQ ID NO: 15) were used to PCR amplify the SPITZ TMD using SEAP/TGFα/Spi/TGFα as the template. The product was cloned into GFP/TGFα/Spi/TGFα using *Eco*RI and *Bbs*-I restriction sites.